REMARKS

Claims 1, 11, 36, 42, 43, 82-88, and 90-93 are pending in the instant application.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance.

I. The Rejection of Claims 1, 11, 36, 42-43, 82-88, and 90-93 under 35 U.S.C. § 103

Claims 1, 11, 36, 42-43, 82-88, and 90-93 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wilson *et al.* (*PNAS* 96: 12833-12838, 1999) in view of Cao *et al.* (*Mol. Microbiol.* 45: 1267-1276, 2002). The Office Action stated:

> [I]t would have been prima facie obvious at the time of applicants' invention to apply the *Bacillus subtilis* strain of Cao et al., to Wilson et al., method for determining the mode of action of an antimicrobial compound in order to provide obtain antimicrobial mode of action results for *B. subtilis* which is known to be resistant to known antimicrobial drugs. One of ordinary skill in the art would have a reasonable expectation of success by exchanging one gram-positive bacterium for another gram-positive bacteria because both bacteria are known in the art to have analyzed on DNA microarrays wherein the hybridization complexes detected in the presence of antimicrobial compounds. Furthermore, no more than routine skill would have been required to exchange the M. tuberculosis of Wilson et al., for the *B. subtilis* of Cao et al., since the ability for pathway characterization is available because complete genome sequences of *B. subtilis* is known along with microarrays containing representatives of each of the gene.

This rejection is respectfully traversed for the reasons of record and further for the reasons stated below.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the *claimed subject matter as a whole* would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. John Deere*, 383 U.S. 1 (1966).

Wilson *et al.* disclose exploring drug-induced alterations in gene expression in *Mycobacterium tuberculosis* by microarray hybridization.

Cao *et al.* disclose antibiotics that inhibit cell wall biosynthesis induce expression of the *Bacillus subtilis* σ^W and σ^M regulons.

Applicants submit that Wilson *et al.* and/or Cao *et al.* do not teach or suggest the instant invention. Wilson *et al.* teach the use of DNA microarrays to characterize the global

transcriptional response of *Mycobacterium tuberculosis* to isoniazid (INH) at concentrations of 0.2 µg or 1 µg of INH per ml, which are above the minimum inhibitory concentration of INH, *i.e.*, 0.02 µg of INH per ml. Cao *et al.* teach the use of DNA microarrays to characterize the global transcriptional response of *Bacillus subtilis* to vancomycin at concentrations 10X the minimum inhibitory concentration.

The Office submits that "no more than routine skill is involved in adjusting the concentration of the claimed process to suit a particular starting material in order to achieve the results taught in the prior art" and "optimization within prior art conditions or through routine experimentation is not patentable". The Office argues that "differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art" on the ground that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Applicants disagree with the Office's asssertion. The issue is whether the the use of sub-inhibitory amounts of an antimicrobial compound amount to invention, or whether such changes would have been obvious to one skilled in the art. The *In re Aller* Court stated: "Normally, it is expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art."

Applicants submit that the utilization of sub-inhibitory amounts of an antimicrobial compound in the claimed methods is inventive on the grounds that (1) one of ordinary skill in the art would not be motivated by the references to arrive at the claimed invention, and (2) the claimed methods produce unexpected results that are different in kind and not merely in degree from the results in the cited references.

First, Applicants assert that, applying a non-rigid Teaching-Suggestion-Motivation (TSM) analysis, one of ordinary skill in the art would not be motivated by the references to to use sub-inhibitory concentrations of an antimicrobial compound based on the cited references. Wilson *et al.* teach the use of isoniazid (INH) at concentrations of 0.2 µg or 1 µg of INH per ml, which are above the minimum inhibitory concentration of INH. Cao *et al.* teach the use of vancomycin at concentrations 10X the minimum inhibitory concentration. In the cases of Wilson *et al.* and Cao *et al.*, sub-inhibitory concentrations were not used or suggested. Moreover, one skilled in the art would recognize that optimization of the

inhibitory range of an antimicrobial compound would involve concentrations above the minimum inhibitory concentration, not sub-inhibitory concentrations. Consequently, Applicants have not optimized the inhibitory range of an antimicrobial compound, but rather use sub-inhibitory concentrations, which do not fall within or overlap concentrations above the minimum inhibitory concentration.

Second, the claimed methods produce unexpected results that are different in kind and not merely in degree from the results in the cited references because the claimed methods utilize sub-inhibitory amounts of an antimicrobial compound that result in the ability to more readily identify primary effects of the antimicrobial compound on genes of the bacterial cell and reduce secondary effects on other genes that can result from using high inhibitor concentrations of the compound. The use of sub-inhibitory concentrations consequently slows the action of the compounds, and limits the expression of genes that are correlated to secondary effects, allowing a predominance of expressed nucleic acids that correlate with the activity of the antimicrobial compound, which is related directly, and primarily, with its mode of action on the cell. Applicants' submit that their results exhibit a superior advantage that a person skilled in the art would have found surprising and unexpected.

Consequently, Wilson *et al.* and/or Cao *et al.* do not teach or suggest a method for determining the mode of action of an antimicrobial compound, comprising: (a) detecting hybridization complexes formed by contacting at least one nucleic acid sample, obtained by culturing cells of a *Bacillus subtilis* in the presence of at least one sub-inhibitory amount of an antimicrobial compound having an unknown mode of action, with a plurality of nucleic acid sequences corresponding to genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate, wherein the presence, absence or change in the amount of the hybridization complexes detected, compared with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode of action, is indicative of the similarity of the mode of actions of the antimicrobial compound and the standard compound; and (b) assigning a mode of action for the antimicrobial compound based on the similarity of values assigned to the hybridization complexes detected in (a) based on the relative amount of hybridization to a second set of hybridization values assigned to the hybridization complexes formed from the second nucleic acid sample, as claimed herein.

For the foregoing reason, Applicants submit that the claims overcome the rejections under 35 U.S.C. § 103 and respectfully request reconsideration and withdrawal of the

rejections.

II. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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